```
=> D HIS
     (FILE 'USPAT' ENTERED AT 14:49:29 ON 20 SEP 96)
L1          2239 S INSULIN LIKE GROWTH FACTOR? OR INSULIN (3A) GROWTH FACTO
R?
L2            28 S AIDS DEMENTIA
L3             2 S L1 AND L2
L4          1949 S ALZHEIMER##
L5            49 S L1 AND L4
L6          2165 S PARKINSON##
L7            31 S L1 AND L6
=> S (INSULIN LIKE GROWTH FACTOR? OR INSULIN (4A) GROWTH FACTOR? OR igf##) (P)
ALZHEIMER##
          7016 INSULIN
       1150532 LIKE

        114882 GROWTH
        364231 FACTOR?
           526 INSULIN LIKE GROWTH FACTOR?
                 (INSULIN(W)LIKE(W)GROWTH(W)FACTOR?)
          7016 INSULIN
        114882 GROWTH
        364231 FACTOR?
          5478 GROWTH FACTOR?
                 (GROWTH(W)FACTOR?)
          1846 IGF##
          1949 ALZHEIMER##
L8          10 (INSULIN LIKE GROWTH FACTOR? OR INSULIN (4A) GROWTH FACTOR?
 OR
                IGF##) (P) ALZHEIMER##
=> D 1-10
```

1. 5,534,615, Jul. 9, 1996, Cardiac hypertrophy factor and uses therefor; Joffre Baker, et al., 530/350; 424/569, 570; 530/380 [IMAGE AVAILABLE]

2. 5,470,949, Nov. 28, 1995, Method for making amino acid glycosides and glycopeptides; Robin L. Polt, 530/322, 327, 328, 329, 330, 331; 562/575; 564/165, 197 [IMAGE AVAILABLE]

3. 5,198,340, Mar. 30, 1993, Assay for free IGF-I, IGF-II, and GH levels in body fluids; Venkat R. Mukku, 435/7.8, 7.9, 7.94, 29, 975; 436/86, 501, 504, 518, 531, 817 [IMAGE AVAILABLE]

4. 5,093,317, Mar. 3, 1992, Treating disorders by application of insulin-like growth factor; Michael E. Lewis, et al., 514/12; 424/556, 570; 514/3, 4, 21, 885, 903 [IMAGE AVAILABLE]

5. 5,017,470, May 21, 1991, Method of diagnosing alzheimer's disease and senile dementia; Chaovanee Aroonsakul, 435/4, 2, 3, 29 [IMAGE AVAILABLE]

6. 4,902,680, Feb. 20, 1990, Treating central nervous system diseases; Chaovanee Aroonsakul, 514/171, 178, 182, 879 [IMAGE AVAILABLE]

7. 4,898,857, Feb. 6, 1990, Treating control nervous system diseases; Chaovanee Aroonsakul, 514/171, 178, 182, 879 [IMAGE AVAILABLE]

8. 4,898,856, Feb. 6, 1990, Method for treating central nervous system diseases; Chaovanee Aroonsakul, 514/171, 178, 182, 879, 903 [IMAGE AVAILABLE]

9. 4,897,389, Jan. 30, 1990, Treating central nervous system diseases; Chaovanee Aroonsakul, 514/171, 178, 182, 879 [IMAGE AVAILABLE]

10. 4,727,041, Feb. 23, 1988, Method of diagnosing Alzheimer's disease; Chaovanee Aroonsakul, 436/8, 87, 500, 811 [IMAGE AVAILABLE]

=> D 9 DATE

L8: 9 of 10

TITLE:	Treating central nervous system diseases		
US PAT NO:	4,897,389 [IMAGE AVAILABLE]	DATE ISSUED:	Jan. 30, 1990
APPL-NO:	07/293,134	DATE FILED:	Jan. 3, 1989
REL-US-DATA:	Continuation of Ser. No. 156,242, Feb. 16, 1988, which is a continuation-in-part of Ser. No. 666,254, Oct. 29, 1984, Pat. No. 4,791,099, and a continuation-in-part of Ser. No. 852,645, Apr. 16, 1986, Pat. No. 4,727,041.		

=> D 9 KWIC

US PAT NO: 4,897,389 [IMAGE AVAILABLE] L8: 9 of 10

ABSTRACT:
A method of treating human suffering from central nervous system diseases, such as **Alzheimer**'s disease, Parkinson's disease, senile dementia. The treatment consists of inducing into the patient's blood stream at least one from the. . . those patients where it has been determined that a low level of growth hormone is present. A method of diagnosing **Alzheimer**'s disease, senile dementia, by the determination of the levels of the hormones somatotropin (human growth hormone) and somatomedin-C (**IGF**-I) after the administration of the Aroonsakul-Allen provocative test is also disclosed. Blood-sera samples are taken at certain time periods after. . .

SUMMARY:

BSUM(4)

The present invention is also directed to a method of diagnosing **Alzheimer**'s Disease in human beings. Presently-used techniques for determining **Alzheimer**'s disease include neuropsychological testing which compares the mental status of the patient relative to a norm, as well as the. . . cognitive dysfunction. Such testing also tests for mood depressions, agitation, irritability, and the like, all of which are symptoms of **Alzheimer**'s disease. Other diagnostic tools and methods are: The use of a brain atlas beam test or EEG (electroencephalogram) which demonstrate. . . order to decide upon the best treatment. The present invention is directed towards the incorporation of a novel diagnosis for **Alzheimer**'s disease and senile dementia, that may be used in conjunction with other standard testing methods, or may be used alone. . . functioning of the peripheral nervous system (PNS) as an aminergic neuronetwork. Furthermore, since the hormone somatomedin-C (often referred to as **IGF**-I, for **insulin**-**like** **growth** **factor**) is directly dependent upon the secretion of HGH by the pituitary gland, there has been established a direct linkage between. . . gland responsible for the HGH production. Generally, the AA provocative test is used by detecting the increase of HGH and **IGF**-I in a blood serum by the use of radioimmunoassay (RIA), which determines the presence or absence or the amounts of. . .

SUMMARY:

BSUM(5)

Somatotropin . . . pituitary gland. This is also known as the human growth hormone (HGH), and is the precursor of the hormone somatomedin-C (**IGF**-I), produced by the liver and kidneys. According to the present invention, it has been discovered that patients suffering from **Alzheimer**'s disease have a deficiency of somatotropin production which leads to a deficiency of somatomedin-C levels, and that exogenous stimulation by a drug to cause increased secretions of HGH in normal human subjects, does not function normally in **Alzheimer**'s patients. Though it has been known to have increased levels of **IGF**-I in the blood with reduced levels of HGH, these instances are rare and can be taken into consideration when determining. . .

DETDESC:

DETD(27)

There . . . provocative test would show a mixed result. In this case, further testing would be required, and a positive determination of **Alzheimer**'s disease would have to be confirmed in conjunction with

other, currently-used, prior art methods of diagnosis, such as EEG testing,. . . conventional methods of diagnosis would be used in conjunction with the method of the present invention. Whereas, both HGH and **IGF**-I deficiency in children may occur, as in dwarfism, such matched deficiency in adults is not known to indicate any other. . .
=> D 1 DATE

L8: 1 of 10

TITLE:	Cardiac hypertrophy factor and uses therefor		
US PAT NO:	5,534,615 [IMAGE AVAILABLE]	DATE ISSUED:	Jul. 9, 1996
APPL-NO:	08/233,609	DATE FILED:	Apr. 25, 1994

=> D 3 DATE

L8: 3 of 10

TITLE:	Assay for free IGF-I, IGF-II, and GH levels in body fluids		
US PAT NO:	5,198,340 [IMAGE AVAILABLE]	DATE ISSUED:	Mar. 30, 1993
APPL-NO:	07/642,509	DATE FILED:	Jan. 17, 1991

=> D 4 DATE

L8: 4 of 10

TITLE:	Treating disorders by application of insulin-like growth factor		
US PAT NO:	5,093,317 [IMAGE AVAILABLE]	DATE ISSUED:	Mar. 3, 1992
APPL-NO:	07/361,595	DATE FILED:	Jun. 5, 1989

=> D 2 KWIC

US PAT NO: 5,470,949 [IMAGE AVAILABLE] L8: 2 of 10

SUMMARY:

BSUM(7)

Abnormalities . . . numerous disease states. Abnormal post-translational modification of the tau protein has been implicated in the formation of neurofibrillary tangles of **Alzheimer**'s disease..sup.8 The antigenic T-epitopes and T.sub.N -epitopes of cell-surface glycopeptides have long been associated with cancer and used as tumor cell markers..sup.9 O-Glycosylated peptide fragments of these two proteins have been synthesized. **Insulin**-**like** **growth** **factor** (**IGF**-1),.sup.10 oncofetal fibronectin Val-Thr-His-Pro-Gly-Tyr (SEQ ID NO: 1) fragment,.sup.11 O-glycosyl-somatostatin analogues,.sup.12 O-glycosyltuftsin analogues,.sup.13 O-glycosyl morphiceptin analogues,.sup.14 glycophorin fragments,.sup.15 and mucin fragments.sup.16. . .

```
=> D HIS
     (FILE 'USPAT' ENTERED AT 14:49:29 ON 20 SEP 96)
L1          2239 S INSULIN LIKE GROWTH FACTOR? OR INSULIN (3A) GROWTH FACTO
R?
L2            28 S AIDS DEMENTIA
L3             2 S L1 AND L2
L4          1949 S ALZHEIMER##
L5            49 S L1 AND L4
L6          2165 S PARKINSON##
L7            31 S L1 AND L6
L8            10 S (INSULIN LIKE GROWTH FACTOR? OR INSULIN (4A) GROWTH FACT
OR?
```

```
FILE 'USPAT' ENTERED AT 14:49:29 ON 20 SEP 96
  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
  *               W E L C O M E   T O   T H E                 *
  *          U. S.   P A T E N T   T E X T   F I L E          *
  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
=> S INSULIN LIKE GROWTH FACTOR? OR INSULIN (3A) GROWTH FACTOR? OR IGF##
          7016 INSULIN
       1150532 LIKE

        114882 GROWTH
        364231 FACTOR?
           526 INSULIN LIKE GROWTH FACTOR?
                 (INSULIN(W)LIKE(W)GROWTH(W)FACTOR?)
          7016 INSULIN
        114882 GROWTH
        364231 FACTOR?
          5478 GROWTH FACTOR?
                 (GROWTH(W)FACTOR?)
           735 INSULIN (3A) GROWTH FACTOR?
          1846 IGF##
L1        2239 INSULIN LIKE GROWTH FACTOR? OR INSULIN (3A) GROWTH FACTOR?
OR
               IGF##
=> S AIDS DEMENTIA
         67226 AIDS
          1625 DEMENTIA
L2          28 AIDS DEMENTIA
                 (AIDS(W)DEMENTIA)
=> S L1 AND L2
L3           2 L1 AND L2
=> D 1-2

1.  5,554,601, Sep. 10, 1996, Methods for neuroprotection; James W.
Simpkins, et al., 514/182, 181 [IMAGE AVAILABLE]

2.  5,475,110, Dec. 12, 1995, Fused Pyrrolocarbazoles; Robert L. Hudkins,
et al., 546/256; 536/17.4; 546/22, 276.7; 548/416, 417, 418, 469 [IMAGE
AVAILABLE]
=> D KWIC

US PAT NO:     5,554,601 [IMAGE AVAILABLE]           L3: 1 of 2

DETDESC:

DETD(10)
 . . .
```

(HBNF)
Growth factors with neurotrophic activity:
Basic fibroblast growth factor
Morrison et al., 1986
(bFGF) Walicke, 1988
Acidic fibroblest **growth** **factor**
Walicke, 1988
(aFGF)
Insulin-**like** **growth** **factors** (**IGF**'s),
Aizenman et al., 1966
insulin Baskin et al., 1987
Epidermal growth factor (EGF)
Fallon et al., 1984
. . .

DETDESC:

DETD(36)

The . . . may be of significant therapeutic use. Other diseases for which estrogen treatment may be effective include Parkinson's disease, Huntington's disease, **AIDS** **Dementia**, Wernicke-Korsakoff's related-dementia (alcohol induced dementia), age related dementia, age associated memory impairment, brain cell loss due to any of the. . .
=> D DATE

L3: 1 of 2

TITLE:	Methods for neuroprotection		
US PAT NO:	5,554,601 [IMAGE AVAILABLE]	DATE ISSUED:	Sep. 10, 1996
APPL-NO:	08/318,042	DATE FILED:	Oct. 4, 1994
REL-US-DATA:	Continuation-in-part of Ser. No. 149,175, Nov. 5, 1993, abandoned.		

=> D 2 KWIC

US PAT NO: 5,475,110 [IMAGE AVAILABLE] L3: 2 of 2

DETDESC:

DETD(49)

As . . . the survival or function of a trophic factor responsive cell. Exemplary trophic factors include Ciliary Neurotrophic Factor (CNTF), basic Fibroblast **Growth** **Factor** (bFGF), **insulin** and **insulin**-**like** **growth** **factors** (e.g., **IGF**-I, **IGF**-II, **IGF**-III), interferons, interleukins, cytokines, and the neurotrophins, including Nerve Growth Factor (NGF), Neurotrophin-3

(NT-3), Neurotrophin-4/5 (NT-4/5) and Brain Derived Neurotrophic Factor. . .

DETDESC:

DETD(58)

A . . . but are not limited to: Alzheimer's; motor neuron disorders (e.g. amyotrophic lateral sclerosis); Parkinson's; cerebrovascular disorders (e.g., stroke, ischaemia); Huntingtons; **AIDS** **dementia**; epilepsy; multiple sclerosis; peripheral neuropathies (e.g., those affecting DRG neurons in chemotherapy-associated peripheral neuropathy); disorders induced by excitatory amino acids;. . .

DETDESC:

DETD(66)

Degeneration, ... neurological disorders, including, but not limited to, Alzheimer's: motor neuron disorders (e.g., ALS); Parkinson's; cerebrovascular disorders (e.g., stroke, ischaemia); Huntingtons; **AIDS** **dementia**; epilepsy; multiple sclerosis: concussive or penetrating injuries of the brain or spinal cord; peripheral neuropathies (e.g., those affecting DRG in. . .

=> D DATE

L3: 1 of 2

TITLE: Methods for neuroprotection
US PAT NO: 5,554,601 [IMAGE AVAILABLE] DATE ISSUED: Sep. 10, 1996
APPL-NO: 08/318,042 DATE FILED: Oct. 4, 1994
REL-US-DATA: Continuation-in-part of Ser. No. 149,175, Nov. 5, 1993, abandoned.

date no good

=> S ALZHEIMER##
L4 1949 ALZHEIMER##
=> S L1 AND L4
L5 49 L1 AND L4
=> D 1-49

1. 5,554,601, Sep. 10, 1996, Methods for neuroprotection; James W. Simpkins, et al., 514/182, 181 [IMAGE AVAILABLE]

2. 5,550,050, Aug. 27, 1996, Method for implanting encapsulated cells in a host; Laura M. Holland, et al., 435/240.2, 240.22, 244, 245 [IMAGE AVAILABLE]

3. 5,545,735, Aug. 13, 1996, Benzo-Fused Lactams promote release of

growth hormone; Richard J. Bochis, et al., 540/490, 523 [IMAGE AVAILABLE]

4. 5,543,328, Aug. 6, 1996, Adenoviruses having modified fiber proteins; Alan McClelland, et al., 435/320.1; 424/93.1, 93.2; 536/23.4, 23.72; 935/22, 32, 57 [IMAGE AVAILABLE]

5. 5,538,722, Jul. 23, 1996, Isolation, growth, differentiation and genetic engineering of human muscle cells; Helen M. Blau, et al., 424/93.21; 435/69.4, 172.3, 240.2 [IMAGE AVAILABLE]

6. 5,536,716, Jul. 16, 1996, Spiro piperidines and homologs which promote release of growth hormone; Meng-Hsin Chen, et al., 514/215, 224.2, 230.5, 248, 278; 540/521, 523; 544/6, 70; 546/17, 18 [IMAGE AVAILABLE]

7. 5,534,615, Jul. 9, 1996, Cardiac hypertrophy factor and uses therefor; Joffre Baker, et al., 530/350; 424/569, 570; 530/380 [IMAGE AVAILABLE]

8. 5,527,527, Jun. 18, 1996, Transferrin receptor specific antibody-neuropharmaceutical agent conjugates; Phillip M. Friden, 424/178.1; 530/391.1, 391.7, 399 [IMAGE AVAILABLE]

9. 5,506,339, Apr. 9, 1996, Octapeptide analogs of somatostatin having threonine at the sixth position; David H. Coy, et al., 530/311, 317, 328; 930/160, 260 [IMAGE AVAILABLE]

10. 5,494,919, Feb. 27, 1996, 2-substituted piperidines, pyrrolidines and hexahydro-1H-azepines promote release of growth hormone; Gregori J. Morriello, et al., 514/323, 318, 319, 322, 324, 326, 362, 363, 365, 372, 394, 396, 414; 544/335; 546/193, 199, 201, 202, 205, 209, 210; 548/127, 128, 205, 214, 253, 306.1, 467, 468 [IMAGE AVAILABLE]

11. 5,492,920, Feb. 20, 1996, Piperidine, pyrrolidine and hexahydro-1H-azepines promote release of growth hormone; Meng H. Chen, et al., 514/323, 318, 319, 322, 324, 326, 362, 363, 365, 372, 394, 396, 414; 544/335; 546/193, 199, 201, 202, 205, 209, 210; 548/127, 128, 205, 214, 253, 306.1, 467, 468 [IMAGE AVAILABLE]

12. 5,492,916, Feb. 20, 1996, Di- and tri-substituted piperidines, pyrrolidines and hexahydro-1H-azepines promote release of growth hormone; Gregori J. Morriello, et al., 514/318, 256, 319, 322, 323, 324, 326, 362, 363, 365, 372, 396, 414; 540/596, 597, 598, 601, 603, 607; 544/335; 546/193, 199, 201, 202, 205, 209, 210; 548/127, 128, 205, 214, 253, 306.1, 467, 468 [IMAGE AVAILABLE]

13. 5,478,807, Dec. 26, 1995, Use of relaxin in the treatment of

bradycardia; Michael Cronin, et al., 514/12; 530/324 [IMAGE AVAILABLE]

14. 5,475,110, Dec. 12, 1995, Fused Pyrrolocarbazoles; Robert L. Hudkins, et al., 546/256; 536/17.4; 546/22, 276.7; 548/416, 417, 418, 469 [IMAGE AVAILABLE]

15. 5,470,949, Nov. 28, 1995, Method for making amino acid glycosides and glycopeptides; Robin L. Polt, 530/322, 327, 328, 329, 330, 331; 562/575; 564/165, 197 [IMAGE AVAILABLE]

16. 5,449,761, Sep. 12, 1995, Metal-binding targeted polypeptide constructs; Benjamin A. Belinka, Jr., et al., 534/10; 530/300, 326, 327, 328, 399, 408; 534/14, 15; 564/18, 23, 26, 27, 28 [IMAGE AVAILABLE]

17. 5,447,959, Sep. 5, 1995, Method of using derivatives of long chain fatty alcohols to treat neuronal degradation; Jacques Borg, 514/725, 690, 693, 703, 715, 763 [IMAGE AVAILABLE]

18. 5,442,043, Aug. 15, 1995, Peptide conjugate; Makoto Fukuta, et al., 530/303, 304, 345, 394, 399, 409 [IMAGE AVAILABLE]

19. 5,438,136, Aug. 1, 1995, Benzo-fused macrocycles promote release of growth hormone; Robert J. Devita, et al., 540/456 [IMAGE AVAILABLE]

20. 5,438,121, Aug. 1, 1995, Brain derived neurotrophic factor; Yves-Alain Barde, et al., 530/399; 435/69.1; 530/350, 387.9, 389.2; 536/23.51 [IMAGE AVAILABLE]

21. 5,434,261, Jul. 18, 1995, Benzo-fused lactams promote release of growth hormone; William R. Schoen, et al., 540/461, 517, 521, 523 [IMAGE AVAILABLE]

22. 5,430,144, Jul. 4, 1995, Benzo-fused lactams promote release of growth hormone; William R. Schoen, et al., 540/461, 517, 521, 523 [IMAGE AVAILABLE]

23. 5,426,177, Jun. 20, 1995, Ciliary neurotrophic factor receptor; Samuel Davis, et al., 530/395, 350, 839 [IMAGE AVAILABLE]

24. 5,374,721, Dec. 20, 1994, Benzo-fused lactams promote release of growth hormone; William R. Schoen, et al., 540/491, 455, 460, 463, 517, 523; 544/51, 105, 354; 546/153, 155 [IMAGE AVAILABLE]

25. 5,364,769, Nov. 15, 1994, Nucleic acid encoding neurotrophic factor four (NT-4), vectors, host cells and methods of production; Arnon Rosenthal, 435/69.1, 69.4, 240.1, 240.2, 320.1; 536/23.5, 23.51 [IMAGE AVAILABLE]

26. 5,317,017, May 31, 1994, N-biphenyl-3-amido substituted benzolactams stimulate growth hormone release; Hyun O. Ok, et al., 514/211, 213; 540/490, 491, 524, 527 [IMAGE AVAILABLE]

27. 5,317,012, May 31, 1994, Human growth hormone induced improvement in depressed T4/T8 ratio; Kenneth A. Kudsk, 514/12, 21 [IMAGE AVAILABLE]

28. 5,310,737, May 10, 1994, Benzo-fused lactams that promote the release of growth hormone; Michael H. Fisher, et al., 514/215; 540/491 [IMAGE AVAILABLE]

29. 5,284,841, Feb. 8, 1994, Benzo-fused lactams promote release of growth hormone; Lin Chu, et al., 514/183, 213, 312, 418; 540/455, 460, 461, 491, 509, 523; 544/52, 105, 354; 546/158; 548/483 [IMAGE AVAILABLE]

30. 5,283,241, Feb. 1, 1994, Benzo-fused lactams promote release of growth hormone; Richard J. Bochis, et al., 514/183, 213, 312, 418; 540/455, 460, 461, 491, 509, 523; 544/52, 105, 354; 546/158; 548/483 [IMAGE AVAILABLE]

31. 5,270,452, Dec. 14, 1993, Pure glia maturation factor; Ramon Lim, et al., 530/399; 435/69.1, 172.3, 252.3, 320.1; 530/350 [IMAGE AVAILABLE]

32. 5,243,094, Sep. 7, 1993, Derivatives of long chain fatty alcohols, their uses, particularly as cytotrophic and cytoprotective molecules, and pharmaceutical compositions containing them; Jacques Borg, 568/822, 667, 668, 824 [IMAGE AVAILABLE]

33. 5,229,500, Jul. 20, 1993, Brain derived neurotrophic factor; Yves-Alain Barde, et al., 514/12; 435/69.1; 530/350, 387.9, 389.2, 399, 412, 413 [IMAGE AVAILABLE]

34. 5,215,969, Jun. 1, 1993, Dopaminergic neurotrophic factor for treatment of Parkinson's disease; Joe E. Springer, et al., 514/21, 2 [IMAGE AVAILABLE]

35. 5,206,235, Apr. 27, 1993, Benzo-fused lactams that promote the release of growth hormone; Michael H. Fisher, et al., 514/213; 540/455, 460, 461, 467, 480, 491, 509, 523; 544/52, 105, 354; 546/157, 158; 548/253, 486 [IMAGE AVAILABLE]

36. 5,198,340, Mar. 30, 1993, Assay for free **IGF**-I, **IGF**-II, and GH levels in body fluids; Venkat R. Mukku, 435/7.8, 7.9, 7.94, 29, 975; 436/86, 501, 504, 518, 531, 817 [IMAGE AVAILABLE]

37. 5,196,315, Mar. 23, 1993, Human neuronal cell line; Gabriele V. Ronnett, et al., 435/29, 240.2, 240.21 [IMAGE AVAILABLE]

38. 5,182,107, Jan. 26, 1993, Transferrin receptor specific antibody-neuropharmaceutical or diagnostic agent conjugates; Phillip M. Friden, 424/179.1, 94.1, 143.1, 178.1; 514/21; 530/387.3, 388.22, 391.1, 391.7, 391.9, 399 [IMAGE AVAILABLE]

39. 5,143,829, Sep. 1, 1992, High level expression of basic fibroblast growth factor having a homogeneous N-terminus; Stewart A. Thompson, et al., 435/69.4, 240.2, 252.3, 252.33, 320.1; 530/399 [IMAGE AVAILABLE]

40. 5,093,317, Mar. 3, 1992, Treating disorders by application of **insulin**-**like** **growth** **factor**; Michael E. Lewis, et al., 514/12; 424/556, 570; 514/3, 4, 21, 885, 903 [IMAGE AVAILABLE]

41. 5,057,494, Oct. 15, 1991, Method for preventing tissue damage after an ischemic episode; Warren D. Sheffield, 514/12, 21 [IMAGE AVAILABLE]

42. 5,017,470, May 21, 1991, Method of diagnosing **alzheimer**'s disease and senile dementia; Chaovanee Aroonsakul, 435/4, 2, 3, 29 [IMAGE AVAILABLE]

43. 4,902,680, Feb. 20, 1990, Treating central nervous system diseases; Chaovanee Aroonsakul, 514/171, 178, 182, 879 [IMAGE AVAILABLE]

44. 4,902,505, Feb. 20, 1990, Chimeric peptides for neuropeptide delivery through the blood-brain barrier; William M. Pardridge, et al., 424/85.7; 514/2, 3, 4; 530/302, 303, 311, 350, 351 [IMAGE AVAILABLE]

45. 4,898,857, Feb. 6, 1990, Treating control nervous system diseases; Chaovanee Aroonsakul, 514/171, 178, 182, 879 [IMAGE AVAILABLE]

46. 4,898,856, Feb. 6, 1990, Method for treating central nervous system diseases; Chaovanee Aroonsakul, 514/171, 178, 182, 879, 903 [IMAGE AVAILABLE]

47. 4,897,389, Jan. 30, 1990, Treating central nervous system diseases; Chaovanee Aroonsakul, 514/171, 178, 182, 879 [IMAGE AVAILABLE]

48. 4,801,575, Jan. 31, 1989, Chimeric peptides for neuropeptide delivery through the blood-brain barrier; William M. Pardridge, 514/4; 424/85.7; 514/2, 3; 530/302, 303, 311, 351; 930/21, 24, 80, 150, 160, 260, DIG.565, DIG.570, DIG.620, DIG.700, DIG.720 [IMAGE AVAILABLE]

49. 4,727,041, Feb. 23, 1988, Method of diagnosing **Alzheimer**'s disease; Chaovanee Aroonsakul, 436/8, 87, 500, 811 [IMAGE AVAILABLE]

=> D 40 KWIC

US PAT NO: 5,093,317 [IMAGE AVAILABLE] L5: 40 of 49
TITLE: Treating disorders by application of **insulin**-**like** **growth** **factor**

ABSTRACT:
Method . . . are at risk of dying, which method includes administering to the mammal an effective amount of a functional derivative of **Insulin**-**like** **Growth** **Factor** I or **Insulin**-**like** **Growth** **Factor** II.

SUMMARY:

BSUM(3)

Insulin-**like** **growth** **factors** (**IGFs**) have been identified in various animal species as polypeptides that act to stimulate growth of cells in a variety of. . . al., Endocrine Rev. 10:68-91 (1989) for reviews), particularly during development (see D'Ercole, J. Devel. Physiol. 9:481-495 (1987) for review). The **IGFs**, each of which has a molecular weight of about 7,500 daltons, are chemically related to human proinsulin: i.e. they possess. . . (2) are connected by a smaller and unrelated C domain. A carboxyl-terminal extension, the D domain, is also present in **IGFs** but is not found in proinsulin.

SUMMARY:

BSUM(4)

Certain polypeptide fragments of the **IGFs** have proven to be useful as antigens to raise antibodies specific for each of the **IGFs** (see, e.g., Japanese Patent Application No. 59065058; Hintz and Liu, J. Clin. Endocr. Metab. 54:442-446 (1982); Hintz et al., Horm. Metab. Res. 20:344-347 (1988)). Using labelled **IGF**-specific antibodies as a probe, **IGF**-I and **IGF**-II (sometimes respectively termed "somatomedin C" and "somatomedin A") have been found in a variety of tissues, including the mammalian central. . . encoding these polypeptides suggests local synthesis in the CNS (see Baskin et al., TINS 11:107-111 (1988) for review). In addition, **IGF**-III (or "brain **IGF**"), a truncated form of **IGF**-I lacking the latter protein's three N-terminal amino acid residues, has been found in fetal and adult human brain (Sara et. . . Natl. Acad. Sci. USA 83:4904-4907 (1986), as well as in colostrum (Francis et al., Biochem. J. 251:95-103 (1988)). Two different **IGF** receptors have been identified in the adult human CNS (Baskin et al., 1988), including in the brain (Sara et al., Neurosci.

Let. 34:39-44 (1982)). In addition, European Patent Application No. 86850417.6 describes evidence for a third type of **IGF** receptor located in human fetal membranes. Complicating research in this area are (1) evidence that the insulin receptor of brain membranes recognizes not only insulin but also the **IGFs**; (2) the finding that one of the two types of adult **IGF** receptors exhibits some affinity for insulin as well as for both **IGF**-I and II, and (3) current uncertainty as to the physiological significance of binding of **IGF**-II to the second type of adult **IGF** receptor (Baskin et al., 1988).

SUMMARY:

BSUM(5)

IGF-I and **IGF**-II appear to exert a stimulatory effect on development or proliferation of a wide range of susceptible cell types (see Daughaday et al., 1989 for review). Treatment with the **IGFs** or with certain polypeptide fragments thereof has been variously suggested as a bone repair and replacement therapy (European Patent Application. . . lactation and meat production in cattle and other farm animals (Larsen et al., U.S. Pat. No. 4,783,524). Each of the **IGFs** also appears to enhance the survival, proliferation and/or neurite outgrowth of cultured embryonic neurons (which, unlike mature neurons, have not. . . the peripheral nervous system (Bothwell, J. Neurosci. Res. 8:225-231 (1982); Recio-Pinto et al., J. Neurosci. 6:1211-1219 (1986)). In addition, the **IGFs** have been shown to affect the development of undifferentiated neural cells: human neuroblastoma tumor cells were shown to respond to added **IGFs** by extending neurites (Recio-Pinto and Ishii, J. Neurosci. Res. 19:312-320 (1988)) as well as by undergoing mitosis (Mattson et al.,. . .

SUMMARY:

BSUM(6)

In vivo studies also support the hypothesis that the **IGFs** play a role in development and differentiation of the immature peripheral and central nervous systems (Sara et al., J. Dev.. . .

SUMMARY:

BSUM(7)

Neurotrophic factors other than the **IGFs** have been proposed as a potential means of enhancing neuronal survival, for example as a treatment for the neurodegenerative diseases. . . skeletal muscle-derived proteins having apparent molecular weights in the

20,000-22,000 dalton and 16,000-18,000 dalton ranges: PCT Application No. PCT/US88/01393), and **Alzheimer**'s disease (using phosphoethanolamine: PCT Application No. PCT/US88/01693). Sara et al., although finding a "significant elevation" in serum and cerebrospinal fluid somatomedin (**IGF**) levels in patients suffering from **Alzheimer**'s disease compared to normal controls, nevertheless conclude:

SUMMARY:

BSUM(8)
Whether somatomedins play a casual (sic) role in the etiology of the dementia disorders of the **Alzheimer** type remains to be determined. However, since somatomedins stimulate the uptake of amino acids into brain tissue, their administration may. . .

SUMMARY:

BSUM(9)

In a report that **IGF**-I, but not **IGF**-II, stimulates the immediate (i.e. within 20 min.) release of acetylcholine from slices of adult rat brain, a process thought to. . .

SUMMARY:

BSUM(10)
[One] of the major deficits in **Alzheimer**'s disease concerns the cholinergic system of the brain, where a reduced synthesis and release of [acetylcholine] has been found. . . . It is of considerable importance to further investigate the role of **IGFs** in neurodegenerative disorders such as **Alzheimer**'s disease . . . (citations omitted).

SUMMARY:

BSUM(11)
Using antibody specific for **IGF**-I to detect an increase in the presence of **IGF**-I in injured peripheral nerves, notably in the non-neuronal cells named "Schwann cells", Hansson et al., Acta Physiol. Scand. 132:35-41, 38,. . .

SUMMARY:

BSUM(12)
Thus, increased **IGF**-I immunoreactivity is observed in regenerating peripheral nerves after any injury and seems to form part of a general reaction pattern,. . . signs of activation, i.e. the granular

endoplasmic reticulum and Golgi complex increased in extent. We thus interpret the increase in **IGF**-I immunoreactivity in the Schwann cells, documented in this study on vibration-exposed nerves, as part of a transient, reactive response beneficial for the early stages of repair processes. . . . We consider the increase in **IGF**-I immunoreactivity to reflect mainly the initial reactions in a chain of events resulting in repair of the injured tissue or organ [although this increase] may be interpreted to reflect disturbed axoplasmic transport [of **IGF**-I molecules], due in part to the diminution of microtubules reported to occur after vibration exposure. (citation omitted)

SUMMARY:

BSUM(13)
Further, Sjoberg et al., Brain Res. 485:102-108 (1989), have found that local administration of **IGF**-I to an injured peripheral nerve stimulates regeneration of the nerve as well as proliferation of associated non-neuronal cells.

SUMMARY:

BSUM(16)

In . . . treatment of neuronal tissues which are suffering from the effects of aging, of injury, or of a disease such as **Alzheimer**'s disease, stroke, epilepsy, amyotrophic lateral sclerosis, or Parkinson's disease, by administering to the mammal an effective amount of a functional derivative, e.g., a fragment or analog of **IGF**-I or of **IGF**-II, alone or in a biologically active combination with another such functional derivative.

SUMMARY:

BSUM(17)

The . . . treatment of neuronal tissues which are suffering from the effects of aging, of injury, or of a disease such as **Alzheimer**'s disease, stroke, epilepsy, amyotrophic lateral sclerosis, or Parkinson's disease, by administering to the mammal an effective amount of a functional derivative of **IGF**-I or of **IGF**-II, preferably a fragment of **IGF**-I or **IGF**-II or, alternatively, an analog of **IGF**-I, of **IGF**-II, or of a fragment of **IGF**-I or **IGF**-II, alone or in a biologically active combination with another such functional derivative.

SUMMARY:

BSUM(19)

The method of the invention uses functional derivatives of **IGF**-I and of **IGF**-II to enhance the survival rate and/or the cholinergic activity of mammalian cells at increased risk of death due to some. . .

SUMMARY:

BSUM(20)

Survival . . . as viable cells, or assaying incorporation of appropriate labelled precursors into mRNA or protein. Where the effect of an added **IGF** or its functional derivative on the functioning of cholinergic neurons is of particular interest, an alternative assay which measures that. . .

SUMMARY:

BSUM(21)

Either approach may be adapted to test the effect of treatment with **IGF** functional derivatives on particular subsets of neurons known to be vulnerable in specific degenerative diseases, such as spinal cord cholinergic neurons in amyotrophic lateral sclerosis. A preliminary screen for polypeptides which bind to the **IGF** receptors may first be employed to indicate likely candidates for the cell survival or cholinergic activity assay; disclosed herein is an **IGF**-I-receptor displacement assay designed for such a purpose. Those polypeptides which appear to promote cell survival or cholinergic activity under one. . .

SUMMARY:

BSUM(23)

The . . . including disorders attributable to a disease or aging of, or injury to, such neuronal cells. The neurotrophic peptides, including the **IGFs** and/or their functional derivatives, are useful for the treatment of neurodegenerative diseases such as **Alzheimer**'s disease, stroke, epilepsy, amyotrophic lateral sclerosis and Parkinson's disease, as well as general age-related neuronal loss, conditions which have proven. . .

DRAWING DESC:

DRWD(2)

FIG. 1 is a graph illustrating the effect of **IGF**-I on the survival

of cholinergic neurons in rat spinal cord cultures.

DRAWING DESC:

DRWD(3)

FIG. 2 is a graph showing the effect of **IGF**-II and **IGF**-III on the survival of cholinergic neurons in rat spinal cord cultures.

DRAWING DESC:

DRWD(4)

FIG. 3 is a graph illustrating the effect of certain synthetic peptide fragments of **IGF**-I and **IGF**-II on the survival of cholinergic neurons in rat spinal cord cultures.

DRAWING DESC:

DRWD(5)

FIG. 4 is a graph depicting the effect on brain ornithine decarboxylase activity of increasing doses of **IGF**-I injected into the brains of immature rats.

DRAWING DESC:

DRWD(6)

FIG. 5 is a graph showing the effect on brain ornithine decarboxylase activity of injection of **IGF**-I or synthetic peptide fragments of **IGFs** into the brains of immature rats.

DRAWING DESC:

DRWD(7)

FIG. 6 is a graph depicting the effect on brain ornithine decarboxylase activity of injection of **IGF**-I into the brains of mature rats.

DETDESC:

DETD(2)

The present invention is directed to the modification of neuroactive polypeptides such as **IGF**-I and **IGF**-II and their functional derivatives, and their use as therapeutics for certain neurological

diseases or disturbances characterized by increased vulnerability of. . . A "neuroactive polypeptide" is defined as a polypeptide which exerts a cell surface-receptor mediated effect on neuronal cells: e.g., the **IGFs**, Nerve Growth Factor (NGF), Epidermal Growth Factor, Fibroblast **Growth** **Factor**, and **insulin**. A "functional derivative" of a polypeptide is a compound which is a fragment or an analog of that molecule and. . . of mediating such effects are disclosed in Remington's Pharmaceutical Sciences (Mack Pub. Co., Easton, Pa., 1980). Although some derivatives of **IGF**-I or **IGF**-II may be inoperative, a person skilled in the art disclosed herein can recognize which are operative and which are not,. . .

DETDESC:

DETD(3)

Some . . . depicted in Table 1, which shows the amino acid sequences (expressed using single-letter abbreviations as defined in Table 2) of **IGF**-I, **IGF**-II, and a number of functional derivatives of **IGF**-I and **IGF**-II. These derivatives were selected for study on the basis of one or more of the following criteria, which are related to the ability to bind to **IGF**-I or **IGF**-II receptors, and thus are useful for identifying additional functional derivatives of the invention: (1) conservation of amino acid sequence among. . .

DETDESC:

DETD(5)

Functional derivatives of the invention include, among others, peptides which vary from the native **IGF** molecules in any one or more of the following ways:

DETDESC:

DETD(12)
7. Linkage of a fragment of **IGF**-I or II with another molecule such as a polypeptide (e.g., another fragment of **IGF**-I or II) or a carbohydrate, by means of a disulfide, peptide, ester or other covalent bond.

DETDESC:

DETD(13)

The . . . . AA.sub.n -R.sub.2, wherein AA.sub.1, AA.sub.2, AA.sub.3, AA.sub.4 . . . AA.sub.n are amino acid residues of the

IGF-peptide subsets or are conservative replacements for them as defined in Table 2, and n is any integer from 5 to 70 for **IGF**-I functional derivatives and 5-67 for **IGF**-II functional derivatives. R.sub.1 is attached to the amino group AA.sub.1 and selected from the group of hydrogen, lower (C.sub.1-6) alkyl,. . .

DETDESC:

DETD(16)

The fragment polypeptides of **IGF**-I and **IGF**-II are subsets of the corresponding **IGF** molecules containing fewer amino acid residues than the native molecules. Preferred are sequences of 5-40 residues and most preferred are. . .

DETDESC:

DETD(20)

As described more fully below, the present invention provides a novel use of **IGF**-I and **IGF**-II and their functional derivatives, as agents for the treatment of diseases or disturbances characterized by an increased risk of cell. . . acetyl transferase assay, both of which are described in detail below. Alternatively, the polypeptides may first be screened by the receptor-**IGF**-I displacement assay described below, which measures the polypeptide's ability to displace labelled **IGF**-I bound to receptors in homogenized brain tissue. This assay has been demonstrated to correlate with the polypeptide's bioactivity as measured by the two enzymatic assays. As described in the examples below, these assays disclose previously unknown bioactivity of **IGF**-I, **IGF**-II, **IGF**-III and some functional derivatives of these molecules. Thus, the peptides of this invention should be useful for administration to humans. . . increased risk of neuronal cell death, as described above. These neurological diseases or disturbances include but are not limited to: **Alzheimer**'s disease, Parkinson's disease, amyotrophic lateral sclerosis, stroke, and concussive or penetrating injuries of the brain or spinal cord.

DETDESC:

DETD(28)

Recombinant human **IGF**-I, **IGF**-II, and **IGF**-III, as well as several chemically synthesized peptides consisting of partial sequences of **IGF**-I or **IGF**-II, were obtained from commercial sources as indicated in Table 1. .sup.125 I-labeled [Threonine.sup.59]**IGF**-I was obtained from Amersham (Arlington Heights, IL). Other peptides consisting

of partial sequences of **IGF**-I or **IGF**-II were chemically synthesized using Fmoc chemistry on a Milligen Biosearch Model 9600 Peptide Synthesizer, and purified on Hewlett-Packard Models 1050. . .

DETDESC:

DETD(29)

Brain . . . at 7800.times.g for 20 minutes and resuspended in 10 volumes of assay buffer. Tissue (50 .mu.l), 100 .mu.l .sup.125 I-[Threonine.sup.59]**IGF**-I (20 pM), and 50 .mu.l of buffer or peptides of varying concentration were added to 96-well plates and incubated on. . . with ice-cold assay buffer using a Brandel cell harvester (Gaithersburg, MD). The filters were removed and the bound .sup.125 I-[Threonine.sup.59]**IGF**-I was measured using a Beckman Model 5500B Gamma Counter.

DETDESC:

DETD(30)

Table 3 summarizes the results of the .sup.125 I-[Threonine.sup.59]**IGF**-I displacement assay utilizing native **IGFs** and **IGF** fragments. The results demonstrate that, while **IGF**-I and **IGF**-III are potent displacers of .sup.125 I-[Threonine.sup.59]**IGF**-I, **IGF**-II is essentially inactive, indicating that the assay is selective for the identification of **IGF**-I-like molecules. In this assay, **IGF**-I(24-41) alone or in combination with **IGF**-II(54-67) were active in displacing .sup.125 I-[Threonine.sup.59]**IGF**-I. **IGF**-II(54-67) alone, and several other fragments listed in Table 3 were not significantly effective displacers of .sup.125 I-[Threonine.sup.59]**IGF**-I.

DETDESC:

DETD(31)

TABLE 3

IGF-I RECEPTOR COMPETITION ASSAY SUMMARY

PEPTIDE (CONC.)	PERCENT MAX. BOUND (SD)	
IGF-I (10 pM)	100	(1.1)
IGF-I (40 nM)	9.6	(0.7)
IGF-II (40 nM)	92.1	(0.7)
IGF-III (40 nM)	17.6	(2.6)

IGF-I(24-41) (100 .mu.M)	44	(7)
IGF-I(24-41) (50 .mu.M)	99	(6)
IGF-I(24-41) (50 .mu.M) + **IGF**-II(54-67) (50 .mu.M)	49	(11)
IGF-II(54-67) (100 .mu.M)	94	(6)
IGF-I(62-70) (100 .mu.M)	83	(20)
IGF-I(30-41) (100 .mu.M)	94	(1.4)
IGF-II(62-67) (100 .mu.M)	83	(21)
IGF-II(33-40) (1 mM)	92	(1.8)

DETDESC:

DETD(33)

Brains . . . the tissue sections were covered with 250 .mu.l of HEPES assay buffer (see Example 1) containing 0.01 nM .sup.125 I-[Threonine.sup.59]**IGF**-I alone or in combination with unlabeled **IGF**-I, **IGF**-II, or synthetic peptide fragments thereof. The sections were incubated at 4.degree. C. for 24 hours and then rinsed in three. . .

DETDESC:

DETD(34)

In this assay, in contrast to the assay described in Example 1, .sup.125 I-[Threonine.sup.59]**IGF**-I binding was potently displaced by both **IGF**-I and **IGF**-II, indicating the utility of this assay for detecting potentially active derivatives of both of these molecules (Table 4). .sup.125 I-[Threonine.sup.59]**IGF**-I binding was displaced by **IGF**-II(33-40), but not by **IGF**-II(54-67).

DETDESC:

DETD(35)

TABLE 4

PEPTIDE (CONC.)	PERCENT MAX. BOUND

IGF-I (4 pM)	91
IGF-I (400 pM)	30
IGF-II (200 nM)	50
IGF-II (400 nM)	23
IGF-II (33-40)(1 mM)	76
IGF-II (33-40)(.10 mM)	82
IGF-II (54-67)(.25 mM)	167
IGF-II (54-67)(.025 mM)	132

DETDESC:

DETD(37)

The activity of **IGF**-I, **IGF**-II, or synthetic peptide derivatives of these molecules was assayed on dissociated cultures of 14-day embryonic rat spinal cord neurons. The. . .

DETDESC:

DETD(38)

In this assay, **IGF**-I was found to produce a substantial, dose-dependent increase in choline acetyltransferase activity (FIG. 1), suggesting that **IGF**-I can dramatically enhance the cholinergic activity of spinal cord cholinergic neurons. Furthermore, **IGF**-II and **IGF**-III were found to be active in the spinal cord assay (FIG. 2). In addition, **IGF**-I(24-41) and **IGF**-II(33-40) were also found to produce a dose-dependent increase in choline acetyltransferase activity, indicating that each peptide is an active **IGF** functional derivative (FIG. 3).

DETDESC:

DETD(40)

The in vivo activity of **IGF**-I, **IGF**-II or synthetic peptide derivatives of these molecules was tested using a biochemical marker for CNS neurotrophic activity, the induction of. . .

DETDESC:

DETD(41)

Sprague-Dawley . . . old; were injected intracerebrally (in the area of the lateral ventricle) with 5 .mu.l of 0.1M phosphate-buffered saline (PBS) containing **IGF**-I, **IGF**-II or a synthetic peptide derivative (1.25-2.5 .mu.g dose, with 6 animals per treatment group). After 6 hours, the brains were. . .

DETDESC:

DETD(42)

Administration of **IGF**-I produced a dose-dependent increase in brain ornithine decarboxylase activity (FIG. 4). In addition, both **IGF**-I(24-41) and **IGF**-II(54-67) increased brain ornithine decarboxylase activity (FIG. 5; these peptides are referred to in FIG. 5 as **IGF**-I (2-4) and **IGF**-I(5-6), respectively).

DETDESC:

DETD(44)

To determine whether the induction of brain ornithine decarboxylase by **IGF**-I was limited to developing animals, **IGF**-I was also injected intraventricularly into the lateral ventricles of adult Sprague-Dawley rats. After 6 hours, the brains were removed, dissected. . . septum, and hippocampus), and then assayed for ornithine decarboxylase activity as described in Example 4. As shown in FIG. 6, **IGF**-I stimulated ornithine decarboxylase activity in all brain regions assayed. This result indicates that **IGF**-related molecules have potential utility in widespread regions of the brain.

DETDESC:

DETD(47)

For global modification of free carboxyl groups, the polypeptide (e.g., NGF, **IGF**-I, **IGF**-II or a functional derivative) would be reacted with excess hexamethylenediamine (HMD) (15.5 g/g total protein) for 30 minutes at room. . .

DETDESC:

DETD(48)

If . . . polypeptide. This protection procedure would be carried out

as follows: Brain tissue containing receptors for the polypeptide of interest (e.g., **IGF**-I) is prepared as described above in Example 1. After incubation with the polypeptide ligand for 2 hours at 4.degree. C.. . .

DETDESC:

DETD(50)

An . . . to the global modification method is to couple polylysine to at least one free carboxyl group on polypeptide (such as **IGF**-I, **IGF**-II, or a functional derivative of either). The procedure follows the method of Shen et al., 1978. For example, polylysine, **IGF**-I and carbodiimide are added in a 1:1:1 ratio in water or buffer for 3 hours at room temperature. The modified. . .

DETDESC:

DETD(56)

A . . . press). The procedure for glycosylation is based on the method of Schwartz et al., 1977, wherein a polypeptide such as **IGF**-I, **IGF**-II, or a functional derivative of either is combined with glucose and NaCNBH.sub.3 in a molar ratio of 1:300:1600 in 200. . .

CLAIMS:

CLMS(1)

We . . .

a mammal, said cells being at risk of dying, said method comprising administering to said mammal an effective amount of **IGF**-I.

CLAIMS:

CLMS(3)

3. . . . the cholinergic activity of cholinergic neurons in a mammal, said method comprising administering to said mammal an effective amount of **IGF**-I.
=> D 40 DATE

L5: 40 of 49

TITLE: Treating disorders by application of **insulin**-**like** **growth** **factor**

US PAT NO: 5,093,317 DATE ISSUED: Mar. 3, 1992

[IMAGE AVAILABLE]

APPL-NO: 07/361,595 DATE FILED: Jun. 5, 1989

=> S PARKINSON##

L6 2165 PARKINSON##

=> S L1 AND L6

L7 31 L1 AND L6

=> D 1-31

1. 5,554,601, Sep. 10, 1996, Methods for neuroprotection; James W. Simpkins, et al., 514/182, 181 [IMAGE AVAILABLE]

2. 5,550,050, Aug. 27, 1996, Method for implanting encapsulated cells in a host; Laura M. Holland, et al., 435/240.2, 240.22, 244, 245 [IMAGE AVAILABLE]

3. 5,538,722, Jul. 23, 1996, Isolation, growth, differentiation and genetic engineering of human muscle cells; Helen M. Blau, et al., 424/93.21; 435/69.4, 172.3, 240.2 [IMAGE AVAILABLE]

4. 5,534,615, Jul. 9, 1996, Cardiac hypertrophy factor and uses therefor; Joffre Baker, et al., 530/350; 424/569, 570; 530/380 [IMAGE AVAILABLE]

5. 5,527,527, Jun. 18, 1996, Transferrin receptor specific antibody-neuropharmaceutical agent conjugates; Phillip M. Friden, 424/178.1; 530/391.1, 391.7, 399 [IMAGE AVAILABLE]

6. 5,523,226, Jun. 4, 1996, Transgenic swine compositions and methods; Matthew B. Wheeler, 435/240.2; 424/9.1; 435/7.23, 172.3, 240.21; 935/70 [IMAGE AVAILABLE]

7. 5,482,706, Jan. 9, 1996, Transmucosal therapeutic composition; Yasutaka Igari, et al., 424/85.7, 85.1, 85.2, 85.4; 514/3, 4, 12, 21 [IMAGE AVAILABLE]

8. 5,475,110, Dec. 12, 1995, Fused Pyrrolocarbazoles; Robert L. Hudkins, et al., 546/256; 536/17.4; 546/22, 276.7; 548/416, 417, 418, 469 [IMAGE AVAILABLE]

9. 5,447,959, Sep. 5, 1995, Method of using derivatives of long chain fatty alcohols to treat neuronal degradation; Jacques Borg, 514/725, 690, 693, 703, 715, 763 [IMAGE AVAILABLE]

10. 5,438,121, Aug. 1, 1995, Brain derived neurotrophic factor; Yves-Alain Barde, et al., 530/399; 435/69.1; 530/350, 387.9, 389.2; 536/23.51 [IMAGE AVAILABLE]

11. 5,426,177, Jun. 20, 1995, Ciliary neurotrophic factor receptor; Samuel Davis, et al., 530/395, 350, 839 [IMAGE AVAILABLE]

12. 5,416,016, May 16, 1995, Method for enhancing transmembrane transport of exogenous molecules; Philip S. Low, et al., 435/240.1; 424/450; 435/172.3, 240.4, 243; 514/2, 44 [IMAGE AVAILABLE]

13. 5,364,769, Nov. 15, 1994, Nucleic acid encoding neurotrophic factor four (NT-4), vectors, host cells and methods of production; Arnon Rosenthal, 435/69.1, 69.4, 240.1, 240.2, 320.1; 536/23.5, 23.51 [IMAGE AVAILABLE]

14. 5,328,844, Jul. 12, 1994, Culture media for mammalian cells; George E. Moore, 435/240.31; 424/531; 435/240.1, 240.2, 240.21, 240.23, 240.3, 244; 514/2, 21 [IMAGE AVAILABLE]

15. 5,317,012, May 31, 1994, Human growth hormone induced improvement in depressed T4/T8 ratio; Kenneth A. Kudsk, 514/12, 21 [IMAGE AVAILABLE]

16. 5,270,452, Dec. 14, 1993, Pure glia maturation factor; Ramon Lim, et al., 530/399; 435/69.1, 172.3, 252.3, 320.1; 530/350 [IMAGE AVAILABLE]

17. 5,243,094, Sep. 7, 1993, Derivatives of long chain fatty alcohols, their uses, particularly as cytotrophic and cytoprotective molecules, and pharmaceutical compositions containing them; Jacques Borg, 568/822, 667, 668, 824 [IMAGE AVAILABLE]

18. 5,229,500, Jul. 20, 1993, Brain derived neurotrophic factor; Yves-Alain Barde, et al., 514/12; 435/69.1; 530/350, 387.9, 389.2, 399, 412, 413 [IMAGE AVAILABLE]

19. 5,215,969, Jun. 1, 1993, Dopaminergic neurotrophic factor for treatment of **Parkinson**'s disease; Joe E. Springer, et al., 514/21, 2 [IMAGE AVAILABLE]

20. 5,196,315, Mar. 23, 1993, Human neuronal cell line; Gabriele V. Ronnett, et al., 435/29, 240.2, 240.21 [IMAGE AVAILABLE]

21. 5,182,107, Jan. 26, 1993, Transferrin receptor specific antibody-neuropharmaceutical or diagnostic agent conjugates; Phillip M. Friden, 424/179.1, 94.1, 143.1, 178.1; 514/21; 530/387.3, 388.22, 391.1, 391.7, 391.9, 399 [IMAGE AVAILABLE]

22. 5,143,829, Sep. 1, 1992, High level expression of basic fibroblast growth factor having a homogeneous N-terminus; Stewart A. Thompson, et al., 435/69.4, 240.2, 252.3, 252.33, 320.1; 530/399 [IMAGE AVAILABLE]

23. 5,108,921, Apr. 28, 1992, Method for enhanced transmembrane transport of exogenous molecules; Philip S. Low, et al., 435/240.1, 243; 514/2, 44; 935/52 [IMAGE AVAILABLE]

24. 5,093,317, Mar. 3, 1992, Treating disorders by application of **insulin**-**like** **growth** **factor**; Michael E. Lewis, et al., 514/12; 424/556, 570; 514/3, 4, 21, 885, 903 [IMAGE AVAILABLE]

25. 5,017,470, May 21, 1991, Method of diagnosing alzheimer's disease and senile dementia; Chaovanee Aroonsakul, 435/4, 2, 3, 29 [IMAGE AVAILABLE]

26. 4,902,680, Feb. 20, 1990, Treating central nervous system diseases; Chaovanee Aroonsakul, 514/171, 178, 182, 879 [IMAGE AVAILABLE]

27. 4,898,857, Feb. 6, 1990, Treating control nervous system diseases; Chaovanee Aroonsakul, 514/171, 178, 182, 879 [IMAGE AVAILABLE]

28. 4,898,856, Feb. 6, 1990, Method for treating central nervous system diseases; Chaovanee Aroonsakul, 514/171, 178, 182, 879, 903 [IMAGE AVAILABLE]

29. 4,897,389, Jan. 30, 1990, Treating central nervous system diseases; Chaovanee Aroonsakul, 514/171, 178, 182, 879 [IMAGE AVAILABLE]

30. 4,843,037, Jun. 27, 1989, Passivation of indium gallium arsenide surfaces; Eli Yablonovitch, et al., 437/235; 148/DIG.48, DIG.61, DIG.118, DIG.119; 257/629, 631; 437/12, 244, 939, 941, 946 [IMAGE AVAILABLE]

31. 4,727,041, Feb. 23, 1988, Method of diagnosing Alzheimer's disease; Chaovanee Aroonsakul, 436/8, 87, 500, 811 [IMAGE AVAILABLE]

=> D DATE

L7: 1 of 31

TITLE:	Methods for neuroprotection		
US PAT NO:	5,554,601 [IMAGE AVAILABLE]	DATE ISSUED:	Sep. 10, 1996
APPL-NO:	08/318,042	DATE FILED:	~~Oct. 4, 1994~~
REL-US-DATA:	Continuation-in-part of Ser. No. 149,175, Nov. 5, 1993, abandoned.		

date no good

=> D 2 DATE

L7: 2 of 31

TITLE:	Method for implanting encapsulated cells in a host		
US PAT NO:	5,550,050 [IMAGE AVAILABLE]	DATE ISSUED:	Aug. 27, 1996
APPL-NO:	08/228,403	DATE FILED:	Apr. 15, 1994

date not good

```
IN ------ Inventor Information
IPC ----- International Classification
OREF ---- Other Publication References Cited
PARN ---- Parent Case Text Data
PD ------ Issue Date
PPDR ---- Number of Drawing Sheets
PPSP ---- Number of Specification Pages
PRIR ---- Foreign Application Priority
PTAN ---- PCT Number
PTFD ---- PCT Filing Date
PTPD ---- PCT Publication Date
PTPN ---- PCT Publication Number
REI ----- Reissue Data
REL ----- Related Application Data
TERM ---- Term Of Patent
TI ------ Title
UREF ---- U. S. Patent References Cited
XA ------ Assistant Examiner
XP ------ Primary Examiner
KEY ----- Keywords Identified for Patent
IF YOU REQUIRE FURTHER HELP, PLEASE CONTACT YOUR LOCAL HELP DESK
ENTER DISPLAY FORMAT (CIT):END
=> D 3 DATE
```

L7: 3 of 31

TITLE:	Isolation, growth, differentiation and genetic engineering of human muscle cells		
US PAT NO:	5,538,722 [IMAGE AVAILABLE]	DATE ISSUED:	Jul. 23, 1996
APPL-NO:	07/748,348	DATE FILED:	Aug. 22, 1991
REL-US-DATA:	Continuation-in-part of Ser. No. 365,374, Jun. 13, 1989, abandoned.		

=> D KWIC

US PAT NO: 5,554,601 [IMAGE AVAILABLE] L7: 1 of 31

SUMMARY:

BSUM(4)

Neurodegenerative . . . Alzheimer's disease. Other examples of chronic neurodegenerative diseases include diabetic peripheral neuropathy, multiple sclerosis, amyotrophic lateral sclerosis, Huntingdon's disease and **Parkinson**'s disease. Not all neurodegenerative diseases are chronic. Some acute neurodegenerative diseases include stroke, schizophrenia, and epilepsy as well as hypoglycemia. . .

DETDESC:

DETD(8)

"Neurodegenerative . . . nervous system or in the central nervous system. Examples of neurodegenerative disorders include: chronic neurodegenerative diseases such as Alzheimer's disease, **Parkinson**'s disease, Huntington's chorea, diabetic peripheral neuropathy, multiple sclerosis, amyotrophic lateral sclerosis; aging; and acute neurodegenerative disorders including: stroke, traumatic brain. . .

DETDESC:

DETD(10)

. . .

(HBNF)

Growth factors with neurotrophic activity:	
Basic fibroblast growth factor	
	Morrison et al., 1986
(bFGF)	Walicke, 1988
Acidic fibroblest **growth** **factor**	
	Walicke, 1988
(aFGF)	
Insulin-**like** **growth** **factors** (**IGF**'s),	
	Aizenman et al., 1966
insulin	Baskin et al., 1987
Epidermal growth factor (EGF)	
	Fallon et al., 1984

. . .

DETDESC:

DETD(36)

The . . . estrogen replacement or supplementation may be of significant therapeutic use. Other diseases for which estrogen treatment may be effective include **Parkinson**'s disease, Huntington's disease, AIDS Dementia, Wernicke-Korsakoff's related-dementia (alcohol induced dementia), age related dementia, age associated memory impairment, brain cell loss. . .

=

Alzheimer's test assay for serum IGF etc

> s 5017470/pn
L1 1 5017470/PN
=> s l1 and IGF?
2092 IGF?
L2 1 L1 AND IGF?
=> d kwic
US PAT NO: **5,017,470** [IMAGE AVAILABLE] L2: 1 of 1

ABSTRACT:
A . . . diagnosing Alzheimer's disease, senile dementia, by the determination of the levels of the hormones somatotropin (human growth hormone) and somatomedin-C (**IGF**-I) after the administration of the Aroonsakul-Allen provocative test is also disclosed. Blood-sera samples are taken at certain time periods after. . .

SUMMARY:

BSUM(4)

The . . . functioning of the peripheral nervous system (PNS) as an aminergic neuronetwork. Furthermore, since the hormone somatomedin-C (often referred to as **IGF**-I, for insulin-like growth factor) is directly dependent upon the secretion of HGH by the pituitary gland, there has been established. . . gland responsible for the HGH production. Generally, the AA provocative test is used by detecting the increase of HGH and **IGF**-I in a blood serum by the use of radioimmunoassay (RIA), which determines the presence or absence or the amounts of. . .

SUMMARY:

BSUM(5)

Somatotropin . . . pituitary gland. This is also known as the human growth hormone (HGH), and is the precursor of the hormone somatomedin-C (**IGF**-I), produced by the liver and kidneys. According to the present invention, it has been discovered that patients suffering from Alzheimer's. . . normal human subjects, does not function normally in Alzheimer's patients. Though it has been known to have increased levels of **IGF**-I in the blood with reduced levels of HGH, these instances are rare and can be taken into consideration when determining. . .

SUMMARY:

BSUM(9)

It . . . the present invention to use any dopaminergic drug,

catecholamine, serotonin, amphetamine, causing immediate excess secretion of the hormones HGH and **IGF**-I, as well as any drug creating the same excess secretion.

DETDESC:

DETD(27)

There . . . conventional methods of diagnosis would be used in conjunction with the method of the present invention. Whereas, both HGH and **IGF**-I deficiency in children may occur, as in dwarfism, such matched deficiency in adults is not known to indicate any other. . .